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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,144	08/21/2001	Glenn R. Larsen	GFN-5213CP6CN	9733

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/935,144	LARSEN ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,29-45 and 54-71* is/are pending in the application.

4a) Of the above claim(s) *1-20,29-45 and 54-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendment of the claims received on 30 March 2007 has been entered. Applicant's remarks received on 30 March 2007 are acknowledged.

Claims 21-28 and 46-53 have been cancelled. Claims 1-20, 29-45 and 54-71 are pending. Claims 1-20, 29-45 and 54-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 58-71 are under examination.

Claim Objection/Rejection Withdrawn

The rejection of claims 58-77 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in response to Applicant's argument and amendment of the claims.

The objection to claim 69 for a typographical error is withdrawn in response to Applicant's amendment of the claim.

Claim Rejections Maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-71 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Applicant argues that the specification identifies a minimal region of SEQ ID NO: 2, amino acids 42-60, which is sufficient to mediate the binding of PSGL-1 to P-selectin. Applicant argues that the results in Figure 30 (Example 13) show that peptides comprising fragments of amino acids 42-60 of SEQ ID NO: 2 are sufficient in inhibit P-selectin binding; even through Example 13 employs a sequence that includes amino acids 42-56 of SEQ ID NO: 2, there is nothing to suggest that these four additional amino acids would prevent the protein from inhibiting P-selectin binding; and it is reasonable to expect that a protein that comprises the amino acids would retain this activity regardless of additional amino acids. Applicant argues that the specification describes a system for assaying the interaction between cells expressing P-selectin and P-selectin ligand, and this system would enable the skilled artisan to measure the inhibitory effects of PSGL-1 fragments, and Example 6 shows the results that are parallel to those of Theoret et al., which employs a different system that more closely mimics the situation *in vivo*. With regard to the Ridger reference, Applicant argues that the claims recite "reducing inflammation" and such reduction does not require the complete cessation of leukocyte rolling; even if some leukocyte rolling occurred after administration, inflammation would still be reduced by the elimination of a percentage of leukocyte rolling. With regard to the non-P-selectin ligand amino acid sequence, Applicant argues that in Example 15, the specification teaches four fusion proteins, each with the Fc portion of an antibody, an arabinogalactan (AGP), a bone morphogenic protein (BMP) or a cytokine. Applicant argues that each of these fusion proteins contains the region of SEQ ID NO: 2 sufficient for mediating P-selectin binding, and it is

reasonable to expect that such fusion proteins would inhibit P-selectin binding regardless of additional amino acids. With regard to the references by Wang, Gasser and Battistini, Applicant argues that these publications demonstrate the claimed compositions are capable of reducing inflammation in a subject. With regard to the reference by Ulbrich, which is a post-filing date publication, Applicant argues that MPEP 2164.05(a) states "in general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling".

Applicant's arguments have been fully considered but have not been found to be persuasive.

The claims are directed to reducing inflammation in a subject having a disparate listing of many diseases by administering a composition comprising a fusion protein which comprises a P-selectin ligand protein fragment comprising the amino acids 42-60 of SEQ ID NO: 2 and a non-P-selectin ligand amino acid sequence chosen from an antibody, an arabinogalactan protein, a BMP, and a cytokine, or by administering a soluble P-selectin ligand protein or a fragment thereof, comprising the amino acids 42-60 of SEQ ID NO: 2 or the amino acids 42-88 of SEQ ID NO: 2.

As indicated previously, Applicant discloses several P-selectin glycoprotein ligand-1 (PSGL-1) fragments and their Fc chimeric fusion proteins, including 253.Fc (amino acids 42-294 of SEQ ID NO: 2), 148.Fc (amino acids 42-189), 47.Fc (amino acids 42-88), and 19.Fc (amino acids 42-60) (Fig. 12). Of these fragments, 19.Fc binds to the P-selectin with a much weaker affinity (e.g., at 1 μg/ml, the polypeptide exhibits little binding) (Fig. 23). Applicant has not provided support that such a low affinity is

sufficient to inhibit PSGL-1/P-selectin interaction *in vivo*. Example 13 does not cure the deficiency because it only shows an *in vitro* binding assay, in which PSGL-1 protein is mixed with Lec-γ1 (P-selectin-Fc) plus the potential inhibitors (Fig. 30) to show competition of the inhibitor for binding to the P-selectin. Further, none of the fragments comprising amino acids 42-60 of SEQ ID NO: 2 is included in Fig. 30. The closest fragment to 19.Fc is a peptide having a sequence of amino acids 42-56 plus a cysteine residue at the C-terminus. The argument that there is nothing to suggest that these four additional amino acids would prevent the protein from inhibiting P-selectin binding and a protein that comprises the amino acids would retain this activity regardless of additional amino acids is not necessarily true. For example, the specification shows that 47.Fc which is a shorter polypeptide than 253.Fc and 148.Fc has a higher P-selectin binding affinity (Fig. 23). Even through the specification shows that neutralizing anti-P-selectin monoclonal antibodies can block the binding between the CHO:P-selectin cells and COS cells which have been co-transfected with PGSL-1 and α 1,3/1,4 fucosyltransferase (3/4FT) (Example 6), which is parallel to those of the Theoret et al. which use a different cell assay system, the specification does not test any of the fragments in the cell assay.

With regard to the Ridger reference, Ridger teaches that leukocyte rolling during inflammation can continue in the absence of optimal P-selectin/PSGL-1 interaction because cells can use an alternative mechanism that involves P-selectin, L-selectin, and sLe^X-bearing ligands; and that L-selectin and a sLeX-bearing ligand support significant leukocyte rolling although such interaction is only revealed after inhibition of

high-affinity P-selectin/PSGL-1 interaction. As stated above, the specification has not shown any support *in vivo* that the recited inhibitors can block the interaction of leukocytes with endothelial cells, and inhibit leukocyte rolling. Given the fact that the inhibitors used in the Ridger reference (e.g., anti-PSGL1, rPSGL-Ig) are potent inhibitors for P-selectin/PSGL-1 interaction, and yet they fail to block leukocyte rolling, one of ordinary skilled in the art would not know whether the claimed molecules can achieve inhibition in leukocyte rolling, and that inhibition is sufficient to lead to a reduction of inflammation in the recited diseases. Further, simply reciting "a therapeutically effective amount", i.e., "sufficient to show a meaningful patient benefit", without more, is not sufficient for a guidance.

With regard to the non-P-selectin ligand amino acid sequence, the claims recite any antibody, BMP or cytokine. Even through Example 15 teaches making such fusions, e.g., 47.Fc, 47.AGP, 47.BMP2, and 47.IL11, the specification does not teach how to use such a broad genus of molecules. For example, how to use a PSGL-1 fragment conjugated to a TNF-α or IL-1β (which promote inflammation, see Ulbrich et al., pp. 642, column 1). Also, what antibodies in addition to the Fc portion can be conjugated to the molecule?

With regard to the references by Wang, Gasser and Battistini, these publications use rPSGL-Ig or anti-PSGL-1 antibodies. As stated above, the specification has not provided sufficient support that the claimed molecules can exhibit activities like rPSGL-Ig or anti-PSGL-11 antibodies.

With regard to using a post-filing date publication, such as the Ulbrich reference, MPEP 2164.05(a) states in the same paragraph, "If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled".

Since the specification has not provided sufficient guidance or working examples as to what PSGL-1 fragments have specific inhibitory activity for P-selectin/PSGL-1 binding, and can be used as an anti-inflammatory agent in a disparate listing of many diseases, the state of the art establishes that cells can use an alternative mechanism for leukocyte rolling during inflammation in the absence of optimal P-selectin/PSGL-1 interaction, and the claims encompass all those diseases with many causes, striking many tissues, and with many different outcomes, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

NO CLAIM IS ALLOWED.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
June 20, 2007

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER